Increases in Hypertension and Blood Pressure during Pregnancy with Increased Bone Lead Levels

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Prior studies have revealed associations of current lead exposure (blood lead) and past lead exposure (bone lead) with risks of hypertension and elevated blood pressure. The authors examined the effects of blood and bone lead on hypertension and elevated blood pressure in the third trimester and postpartum among 1,006 women enrolled in Los Angeles prenatal care clinics between 1995 and 2001. The authors measured bone lead concentration by K-shell x-ray fluorescence in the tibia (mean = 8.0 µg/g (standard deviation (SD) 11.4)) and calcaneus (heel) (mean = 10.7 µg/g (SD 11.9)). Geometric mean prenatal and postnatal blood lead levels were 1.9 µg/dl (geometric SD +3.6/–1.0) and 2.3 µg/dl (geometric SD +4.3/–1.2), respectively. For each 10-µg/g increase in calcaneus bone lead level, the odds ratio for third-trimester hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) was 1.86 (95% confidence interval (CI): 1.04, 3.32). In normotensive subjects, each 10-µg/g increase in calcaneus bone lead level was associated with a 0.70-mmHg (95% CI: 0.04, 1.36) increase in third-trimester systolic blood pressure and a 0.54-mmHg (95% CI: 0.01, 1.08) increase in diastolic blood pressure. Tibia bone lead concentration was not related to hypertension or elevated blood pressure either in the third trimester or postpartum, nor was calcaneus bone lead related to postpartum hypertension or elevated blood pressure. Past lead exposure influences hypertension and elevated blood pressure during pregnancy. Controlling blood pressure may require reduction of lead exposure long before pregnancy.

blood; blood pressure; bone and bones; lead; pregnancy

Abbreviation: CI, confidence interval.

Editor’s note: An invited commentary on this article appears on page 1088.

Elevated blood pressure or hypertension presents special risks to women, especially during pregnancy. Hypertension is...
the most frequent complication of pregnancy, comprising 5–10 percent of the total (1). Although physicians distinguish among preeclampsia and eclampsia, chronic essential hypertension during pregnancy, and acute or transient hypertension, the origins of these hypertensive disorders remain unknown, and treatments are not based on correcting underlying causes (2).

All forms of hypertension during pregnancy threaten the development or life of the fetus, and some, notably eclampsia, threaten the mother’s life as well. Preeclampsia is identified by an elevated blood pressure (≥140/90 mmHg) in the second half of pregnancy with proteinuria and, variously, reduced platelets, an elevated serum creatinine level, and headaches or other central nervous system symptoms, among others. Preeclampsia may progress to eclampsia, in which the mother suffers seizures. A necessary but not sufficient feature of preeclampsia is pregnancy hypertension. Other predictors of increased risk are higher body mass index (≥3), nulliparity (4), diabetes mellitus, preexisting chronic hypertension (5), and elevated blood pressure earlier in pregnancy (6–9).

Having a higher blood pressure within normotensive limits in the second half of pregnancy is associated with reduced birth weight (10). Lowering a woman’s blood pressure during pregnancy, even in cases of mild hypertension, may decrease the risk of perinatal mortality and abruptio placentae, though treatment with antihypertensive medications may also present increased risk to the fetus (11, 12).

Lead exposure is a risk factor for hypertension and elevated blood pressure in the general population. Although there are many epidemiologic studies that show a positive association between blood pressure and lead exposure (13–19), inconsistencies among studies have provoked controversy regarding the effect (see Hertz-Picciotto and Croft (20) for a review). Two large-sample studies reported a small but highly significant relation between blood lead concentrations in the umbilical cord (21) and in third-trimester pregnant women (19) and maternal blood pressure during pregnancy.

Recently, small but significant associations between bone lead concentration and hypertension risk were found in an aging male sample (22) and in a middle-aged to aging female sample (23), both in the absence of a significant concurrent blood lead effect. These authors suggested that, since bone lead reflects the accumulation of years to decades of lead exposure, the increased risk of hypertension associated with a higher bone lead concentration might be the result of damage due to past lead exposure.

Gaining control over any factor that can reduce the risk of pregnancy hypertension and elevated blood pressure will improve pregnancy outcomes. The purpose of the present work was to define the relations of both maternal bone lead concentration and blood lead concentrations in the third trimester of pregnancy and postdelivery with blood pressure and risk of hypertension during and after pregnancy.

MATERIALS AND METHODS

Study population

We recruited a total of 3,473 women in their third trimester of pregnancy who were enrolled in the prenatal care programs of the King-Drew Medical Center and its associated clinics in Los Angeles, California, from June 1995 to May 2001. King-Drew Medical Center, operated by Los Angeles County, serves South Central Los Angeles, which for decades has been one of the most economically depressed areas in the state of California. Most of the patients are immigrants, are Latino or African-American, and have no medical insurance.

Only 1,006 of these subjects returned for the postpartum phase, a mean of 10.0 weeks (standard deviation 1.9) after delivery. All 1,006 subjects returned within 18 weeks. Subjects were between the ages of 15 and 44 years. We excluded from these analyses all subjects with documented renal disease (n = 66), cardiovascular disease (n = 22), diabetes (n = 147), or extreme postnatal obesity (a body mass index (weight/height/2) greater than 40) (n = 32), as well as subjects who used stimulant drugs from the amphetamine and cocaine families (n = 5) during either phase of this study. We also excluded two subjects with pre- or postdelivery blood lead concentrations greater than 5 geometric standard deviations above the geometric mean of the rest of the sample. An additional 74 subjects had missing data on one or more of the pre- or postnatal dependent or independent variables and were excluded. Some subjects met more than one exclusion criterion. Of the excluded cases, 11 had hypertension according to criteria described in the “Statistics” section below, during either the prenatal phase or the postnatal phase of the study. Of the 667 retained cases, 31 met our criteria for hypertension.

The subjects’ treating physicians were notified at both stages of the study if blood lead levels exceeded 10 µg/dl (0.48 µmol/liter) (the upper limit considered safe for pregnant women by the Lead Surveillance Unit of the Los Angeles County Health Department) or if measured blood pressure exceeded 140/90 mmHg.

The study protocol and all materials were reviewed and approved by the King-Drew Institutional Review Board, and all subjects signed approved informed consent forms before joining the study.

Questionnaires

Experienced bilingual interviewers administered the screening questionnaire as a structured interview at recruitment during the third trimester of pregnancy. Subjects elected to receive either the English or the Spanish version. The same interviewers similarly administered the risk questionnaire at the postdelivery session while bone lead concentration (see below) was being measured. These questionnaires allowed us to gather basic socioeconomic and demographic data and information on medical and reproductive history, history of lead exposure, and dietary habits. Risk factors assessed included work and hobby histories, use of leaded paint and ceramic ware, and consumption of pica, cigarettes, alcohol, and other drugs and medications. The questionnaires recorded detailed information on the subject’s medical history, with an emphasis on past and present pregnancies, diabetes, and cardiovascular, renal, thyroid, and parathyroid diseases. The questionnaires were used in previous studies and have been described in previously published articles (19, 24, 25).

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Blood lead measurements

We drew venous blood into blue-top (trace-metal-free) Vacutainers (Becton Dickinson, Franklin Lakes, New Jersey) with heparin after cleaning the venipuncture site at the end of each scheduled subject visit. We analyzed the blood samples for lead concentration using the Perkin Elmer 4100ZL Zeeman atomic absorption spectrometer (Perkin Elmer, Wellesley, Massachusetts) with a graphite furnace at the study’s toxicology laboratory (Environmental Research Center, Charles R. Drew University of Medicine and Science, Los Angeles, California). We analyzed every sample in duplicate and used the mean of the two values. The study’s laboratory has participated successfully in the Wisconsin State Laboratory of Hygiene proficiency testing program and the College of American Pathology’s blood lead quality-assurance program for more than 6 years, with no out-of-bounds results. Data on the quality control, accuracy, and precision of the blood lead analyses have been previously published (24, 25).

The detection limit for blood lead concentration was 0.4 µg/dl (0.02 µmol/liter), since coefficients of variability for measurements below this value regularly exceeded 15 percent. All blood lead concentrations recorded below the detection limit (n = 8) were assigned the value of 0.2 µg/dl (0.01 µmol/liter).

Blood pressure measurements

We measured sitting systolic and diastolic blood pressure using a Colin Press Mate (model BP-8800; Colin Medical Instruments Corporation, San Antonio, Texas) automated cuff-inflation instrument. We calibrated the instrument every 6 months during data collection against a mercury sphygmomanometer reserved for calibration use. The accuracy of the instrument remained within ±1 mmHg of the calibration standard.

After providing informed consent and completing the screening questionnaire interview, the subject remained seated while her blood pressure was measured, 30–45 minutes after being introduced to the interviewer. Postdelivery blood pressure measurements were made during bone lead measurement, also after the subject had been seated for 30–45 minutes. We made the measurements with cuff size selected according to subject’s upper arm diameter and with the right arm elevated to heart height. Three consecutive measurements were made at 3-minute intervals. Pearson correlations among replicate pairs of systolic and diastolic blood pressure measurements averaged 0.81 and 0.71, respectively. The mean unsigned difference among the replicate pairs averaged 4.8 mmHg for systolic measurements and 4.2 mmHg for diastolic measurements. We used the means of the three consecutive measurements in the analyses.

Bone lead measurement

We measured bone lead concentrations at the midtibia (predominantly cortical bone) and midcalcaneus (predominantly trabecular bone) with a 109Cd K-shell x-ray fluorescence system that has been described previously (25–27). Briefly, photons emitted from the decay of 109Cd (88 keV) excite lead atoms within the bone matrix, causing them to emit characteristic x-rays. The amount of coherent scattering of the 88-keV 109Cd photons is proportional to the amount of bone mineral. Because the lead x-ray signal is normalized to the coherent signal, the measurement has units of micrograms of lead per gram of bone mineral (µg/g). The technique allows estimation of the error of measurement, which is an underestimate of the standard deviation of replicate measurements (28). Because of measurement error, the measured bone lead concentration may be negative, especially in cases with a low bone lead level or a thick layer of fat and skin overlying the measurement site. We measured bone lead concentration only postnatally to avoid exposing the fetus to radiation.

Statistics

We used Stata (Stata Corporation, College Station, Texas) and SPSS (SPSS, Inc., Chicago, Illinois) software to manage the data and perform descriptive and inferential statistical tests. We used t tests for independent samples and Fisher’s exact tests to determine possible selection bias between subjects eligible for inclusion in the data set and those not eligible. Blood lead values were natural log-transformed to normalize the variable for all statistical procedures. Bone lead data had an approximately normal distribution; that is, the distribution of bone lead values in the sample was bilaterally symmetric about the mean value, though there was overrepresentation of subjects with bone lead concentrations around the mean as compared with the tails. In other words, the distributions had significant kurtosis compared with the normal distribution. We constructed two dichotomous hypertension variables (third trimester and postpartum) from the blood pressure measurements using a systolic cutoff of ≥140 mmHg and a diastolic cutoff of ≥90 mmHg. Any subject with either systolic blood pressure or diastolic blood pressure above the relevant cutoff had hypertension.

Since nearly 80 percent of the subjects were immigrants, predominantly from Latin America, and over 80 percent of the subjects were seeking medical attention for the pregnancy for the first time during the third trimester, we were unable to determine either family history of hypertension or preexisting hypertension. We used postnatal hypertension as a proxy for preexisting hypertension and added the variable to the prenatal hypertension model. Since none of the subjects with hypertension reported using alcohol, the hypertension models did not include alcohol use as a covariate. We used the dichotomous hypertension variable in a logistic regression analysis to determine odds ratios for blood lead and bone lead concentration in accounting for hypertension during and after pregnancy, after adjusting the data for body mass index, age, parity, smoking, and educational level. Hypertension after pregnancy was similarly defined.

We then removed from the database all subjects with a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg during or after pregnancy. We constructed multiple regression models with blood pressure as the dependent variable to determine whether blood lead
and bone lead were independently associated with variations in normal blood pressure.

The two bone lead measurements and the period-specific blood lead measurement were simultaneously entered into all models. When diagnostic tests indicated the need, robust standard errors were calculated and used in place of standard errors for calculation of confidence intervals. Partial residual plots of lead variables versus blood pressure were constructed.

RESULTS

Subjects who returned for postpartum testing used significantly more alcohol, were more often immigrants, were significantly older, had less education, and had a higher body mass index than subjects who did not return. Returning subjects eligible for inclusion in the data set were significantly older, used less alcohol, had a lower body mass index, had lower blood pressure, tended to be pregnant for the first time, and more often nursed their babies in comparison with subjects not eligible for inclusion (table 1). Many of the differences among the groups, though significant, were small. Some of the significant differences among groups, notably body mass index and blood pressure, were expected as a result of the specific exclusion criteria used. Such differences are not expected to have limited the conclusions drawn in this study.

No cases of preeclampsia were noted during pregnancy, since the exclusion criteria, particularly body mass index and diabetes, removed the most likely candidates.

Figure 1 shows box plots of bone lead measurements divided into plots of subjects with and without third-trimester and postpartum hypertension. Only calcaneus lead concentration in third-trimester hypertensive subjects appeared elevated in comparison with nonhypertensive subjects. The only systematic increase in frequency of hypertension with increasing quartile of bone lead concentration was seen with calcaneus lead in prenatal hypertensive subjects (table 2). Unadjusted odds ratios for each 10-µg/g increase in calcaneus lead level were 1.79 (95 percent confidence interval (CI): 1.21, 2.66) for third-trimester hypertension and 1.23 (95 percent CI: 0.91, 1.65) for postpartum hypertension. Unadjusted odds ratios for third-trimester and postpartum hypertension for each 10-µg/g increase in tibia lead level were 0.98 (95 percent CI: 0.21, 1.66) and 1.13 (95 percent CI: 0.81, 1.58), respectively.

Logistic regression analysis of prenatal hypertension adjusted for control variables showed that for all the lead measures, only calcaneus (trabecular bone) lead concentration was significantly related to hypertension risk (table 3). For each 10-µg/g increase in calcaneus lead concentration, the odds ratio for hypertension in the third trimester of pregnancy was 1.86 (95 percent CI: 1.04, 3.32). Neither of the bone lead measures nor blood lead was significantly related to postnatal hypertension risk (table 3).

Regression analysis of third-trimester diastolic and systolic blood pressure in normotensive subjects using blood and bone lead concentrations showed similar results (table 4). Of all the lead measures, only calcaneus lead concentration was significantly related to prenatal blood pressure. For every 10-µg/g increase in calcaneus lead concentration, there was an increase of 0.70 mmHg (95 percent CI: –0.03, 1.36) in systolic blood pressure (figure 2) and an increase of 0.54 mmHg (95 percent CI: 0.01, 1.58) in diastolic blood pressure. Neither bone lead measure was significantly related to increased postnatal blood pressure (table 4). Increased postnatal blood lead concentration was significantly associated with decreased postnatal systolic and diastolic blood pressure (figure 3).

DISCUSSION

Interpretation of these results must take the study design into account. This was a cohort study, not a case-control study. We measured the prevalence, not incidence, of hypertension. Furthermore, the study was designed from the outset not to recruit pregnant women with hypertension but to study the effects of body lead burden on blood pressure during pregnancy. We took advantage of cases of hypertension discovered during and after pregnancy combined to study lead factors associated with prenatal and postnatal hypertension in logistic regression analyses.

Blood pressure normally increases as the third trimester of pregnancy progresses. A spurious positive relation between calcaneus lead and gestational age at the time of prenatal blood pressure measurement could account for the observed relation between bone lead and blood pressure. Using quartiles of calcaneus lead (see table 2) and third-trimester gestational age in analysis of variance, we found a nonsignificant negative relation ($F(3,664) = 1.26; p = 0.29$).

Bone lead and blood pressure

Alternate analyses. Ordinary logistic regression often underestimates the probability of rare events (in the present case, 1.6 percent of the working prenatal sample), leading to biased estimates of coefficients even with sample sizes in the thousands (29). Although the odds ratio for an increase in calcaneus bone lead was significant for third-trimester hypertension, it is likely that the rarity of hypertension in the present cohort biased this estimate. We used a modified logistic regression technique (30) that corrects for this bias and calculated an alternate calcaneus bone lead odds ratio for prenatal hypertension of 1.68 (95 percent CI: 1.01, 2.78).

Use of postnatal hypertension as a proxy for preexisting hypertension may overcontrol for this factor. We constructed an alternate third-trimester hypertension model without the postnatal hypertension variable. The odds ratio for a 10-µg/g increase in calcaneus bone lead level in the alternate model was 2.09 (95 percent CI: 1.28, 3.41).

All methods of estimation suggested a significant effect of calcaneus bone lead concentration on risk of hypertension during pregnancy.

Comparison with other studies. Two published studies, one of women in late middle age (23) and the other of elderly men (31), found significant associations between trabecular bone lead concentration and risk of hypertension. Both studies used patella for the trabecular bone measurement, whereas the present study used calcaneus for the trabecular bone measurement. Increased risk of hypertension in women
was found concurrently with bone lead measurement, whereas heightened hypertension risk in the men was found only several years after bone lead measurement in those who had no hypertension at the time of measurement.

**TABLE 1. Characteristics of subjects included in and excluded from a study of lead levels and hypertension during and after pregnancy, King-Drew Medical Center prenatal care clinics, Los Angeles, California, 1995–2001**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subject status</th>
<th>No.‡</th>
<th>%</th>
<th>Mean</th>
<th>p value*</th>
<th>No.‡</th>
<th>%</th>
<th>Mean</th>
<th>p value†</th>
<th>No.‡</th>
<th>%</th>
<th>Mean</th>
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</thead>
<tbody>
<tr>
<td>Nursing (postpartum)</td>
<td>Recruited but did not return (n = 2,467)</td>
<td>712</td>
<td>51.1</td>
<td>&lt;0.09</td>
<td>282</td>
<td>45.0</td>
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<td>Smoking (current)</td>
<td>Recruited but did not return (n = 2,467)</td>
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<td>51.1</td>
<td>&lt;0.09</td>
<td>282</td>
<td>45.0</td>
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<td>Alcohol use (current)</td>
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<td>51.1</td>
<td>&lt;0.09</td>
<td>282</td>
<td>45.0</td>
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<td>Primiparity</td>
<td>Recruited but did not return (n = 2,467)</td>
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<td>51.1</td>
<td>&lt;0.09</td>
<td>282</td>
<td>45.0</td>
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<tr>
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<td>51.1</td>
<td>&lt;0.09</td>
<td>282</td>
<td>45.0</td>
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<td>Immigrant</td>
<td>Recruited but did not return (n = 2,467)</td>
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<td>51.1</td>
<td>&lt;0.09</td>
<td>282</td>
<td>45.0</td>
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<tr>
<td>Age (years)</td>
<td>Recruited but did not return (n = 2,467)</td>
<td>712</td>
<td>51.1</td>
<td>&lt;0.09</td>
<td>282</td>
<td>45.0</td>
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<tr>
<td>Education (years)</td>
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<td>45.0</td>
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<td>Income &lt;$20,000/year</td>
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<td>&lt;0.09</td>
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<td>45.0</td>
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<td>Body mass index¶</td>
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<td>45.0</td>
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<td>Blood lead# (µg/dl)</td>
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<td>51.1</td>
<td>&lt;0.09</td>
<td>282</td>
<td>45.0</td>
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<td>&gt;10 µg/dl†</td>
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<td>Bone lead (µg/g)</td>
<td>Recruited but did not return (n = 2,467)</td>
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<td>51.1</td>
<td>&lt;0.09</td>
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</table>

* Probability for comparison between subjects returning for postpartum testing and subjects not returning (t tests for continuous variables, Mann-Whitney U test for education, Fisher's exact test for dichotomous variables, and chi-squared test for multiple categorical variables).

† Probability for comparison between subjects returning for postpartum testing and excluded returning subjects (t tests for continuous variables, Mann-Whitney U test for education, Fisher's exact test for dichotomous variables, and chi-squared test for multiple categorical variables).

‡ Numbers given may differ from category totals because not all subjects provided complete data on each variable.

§ Numbers in parentheses, standard deviation.

¶ Weight (kg)/height (m)².

# Geometric mean and geometric standard deviation.

** Conversion: 10 µg/dl = 0.483 µmol/liter.**
elderly men (22) cited above, as well as in a group of men occupationally exposed to lead whose ages spanned most of the adult years (32).

These studies differed from the present study in terms of the sex and age of the subjects, the range of bone lead values, the specific bone measured for the trabecular bone sample, and the blood pressure cutoff values defining hypertension, though the ages and ranges of bone lead and blood lead values among studies largely overlap. Several different explanations may account for the similarities and differences in the results of all of these studies.

Two studies, ours and that of Korrick et al. (23), found significant associations of trabecular bone lead with concurrent hypertension in women. In the latter study, the coefficient describing the effect of trabecular bone lead concentration on hypertension in premenopausal women was 19 percent of the same coefficient in postmenopausal women. Thus, hypertension in women undergoing hormonal change known to alter bone metabolism, as occurs during menopause and pregnancy, is associated with trabecular bone lead. Since even older men suffer bone loss, the association of trabecular bone lead with development of future hypertension found by Cheng et al. (31) also suggests that during periods of altered bone metabolism, particularly bone loss, increasing trabecular bone lead content may play a role in increasing risk of hypertension.

Trabecular bone lead is more easily mobilized from bone than is lead from cortical bones, since the characteristic biologic “residence time” of lead in calcaneus is calculated to range from 11 years to 29 years (95 percent CI), whereas the residence time of lead in tibia has been estimated to range from 16 years to 98 years (95 percent CI) (33). Thus, during times of high calcium stress, more lead may be mobilized from trabecular bone into the blood than from cortical bone, leading to the significant calcaneus lead–blood pressure and calcaneus lead–hypertension relations seen in the third trimester of pregnancy. When the calcium stress is removed and bone metabolism decreases after pregnancy, less lead is mobilized from trabecular bone, leading to the significant calcaneus lead–blood pressure and calcaneus lead–hypertension relations seen in the third trimester of pregnancy. A recent report that bone resorption in older men especially influences release of trabecular bone lead (34) supports this idea.

The proposed bone lead–blood lead pathway described above supposes that there may be a direct and immediate effect of circulating lead in blood on blood pressure. While a blood lead effect on blood pressure and/or hypertension has been noted in the work discussed in this paper's introduction,

FIGURE 1. Box-and-whisker plots of bone lead concentration by hypertension status in the third trimester and postpartum (n = 668), King-Drew Medical Center prenatal care clinics, Los Angeles, California, 1995–2001. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Only calcaneus lead concentration in the third trimester was generally higher for subjects with hypertension than subjects without hypertension. Boxes show the median and interquartile range; T-shaped bars show ±1.5 times the interquartile range; circles show outliers.
where, within minutes, over 99 percent is sequestered in the red blood cells. Lead in serum may be readily transported to target organs and may constitute the majority of the bioavailable lead in circulation. Lead from exogenous sources, such as ingested or respired lead, enters the body in a discontinuous fashion, depending upon the exposure pattern. The rapid take-up of lead by erythrocytes suggests that elevated lead concentrations in the serum will be episodic, varying as lead is absorbed from the environment, distributed to various compartments, and eliminated from the body. Lead from an endogenous source, such as bone, may present a more constant inflow into serum than lead from exogenous sources. Constant release of lead from bone into serum may elevate the serum lead fraction continuously over extended periods of time, thus leading to greater transfer of lead from serum to target organs than occurs with the episodic intake of exogenous lead, even given equal whole-blood lead levels in the two cases. Since serum lead concentration is significantly associated with bone lead concentration (35), a direct and immediate bone lead effect on blood pressure/hypertension mediated by lead in serum is plausible. However, to our knowledge, a demonstration of greater bioavailability of serum lead over whole-blood and bone lead has not been published to date.

An alternate explanation for the associations between bone lead and blood pressure/hypertension focuses on cumulative bone lead concentration over years of lead exposure. Subjects with a higher bone lead concentration, all other factors being equal, have a history of longer or higher exposure to lead. Past higher lead exposure could have damaged organ systems involved in blood pressure control, such as kidney function (36). However, it is difficult to reconcile this view with results giving different roles to lead in cortical and trabecular bone and the role of current bone metabolic status in the bone lead–blood pressure/hypertension association noted in the literature.

**Blood lead and blood pressure**

Previous research leads to the expectation that where there is a significant effect of lead on blood pressure, the relation is positive. In the larger cohort from which the current sample was drawn, we found that increasing prenatal blood pressure was associated with increasing prenatal blood lead concentration (19). The significant negative association between postnatal blood pressure and postnatal bone lead concentration is without precedent in the literature, though we know of no other published studies examining this relation in postpartum women.

The return of various cardiovascular parameters, such as systemic vascular resistance, end-diastolic volume, stroke volume, and cardiac volume, to prepregnancy values extends to at least 1 year postpartum (37). Altered postpartum cardiovascular function may in some way interact with circulating lead to produce the inverse postpartum blood lead–blood pressure relation.

We tested a number of possible confounding factors or effect modifiers to try to determine whether changes in blood lead and body mass index from the third trimester to postpartum or third-trimester blood pressure could play a role in

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**TABLE 3. Adjusted* odds ratios for hypertension in the third trimester and postpartum according to blood and bone lead concentrations among pregnant women attending King-Drew Medical Center prenatal care clinics (n = 668), Los Angeles, California, 1995–2001**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Third trimester</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural log blood lead (µg/dl)</td>
<td>0.75 (0.21, 2.65)</td>
<td>1.24 (0.64, 2.42)</td>
</tr>
<tr>
<td>Tibia lead (10 µg/g)</td>
<td>0.98 (0.92, 1.04)</td>
<td>1.00 (0.96, 1.04)</td>
</tr>
<tr>
<td>Calcaneus lead (10 µg/g)</td>
<td>1.86 (1.04, 3.32)</td>
<td>1.22 (0.86, 1.73)</td>
</tr>
</tbody>
</table>

* Data were adjusted for postpartum hypertension, education, immigrant status, current smoking, parity, age, and body mass index. Postpartum hypertension was dropped as a covariate for the postpartum analysis. Alcohol was not used to adjust odd ratios, since no hypertensive subjects reported using alcohol.

† OR, odds ratio; CI, confidence interval.

‡ Conversion: 10 µg/dl = 0.483 µmol/liter.

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**TABLE 2. Frequency of hypertension among pregnant women attending King-Drew Medical Center prenatal care clinics, by quartile of bone or blood lead concentration, Los Angeles, California, 1995–2001**

<table>
<thead>
<tr>
<th>Quartile of lead concentration (range given in parentheses)</th>
<th>No. with hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Third trimester</td>
</tr>
<tr>
<td>Calcaneus (µg/g)</td>
<td></td>
</tr>
<tr>
<td>1 (~30.6 to 3.0)</td>
<td>2</td>
</tr>
<tr>
<td>2 (3.1 to 10.0)</td>
<td>0</td>
</tr>
<tr>
<td>3 (10.1 to 18.7)</td>
<td>4</td>
</tr>
<tr>
<td>4 (18.8 to 49.9)</td>
<td>5</td>
</tr>
<tr>
<td>Tibia (µg/g)</td>
<td></td>
</tr>
<tr>
<td>1 (~33.7 to 0.9)</td>
<td>4</td>
</tr>
<tr>
<td>2 (1.0 to 8.0)</td>
<td>3</td>
</tr>
<tr>
<td>3 (8.1 to 16.1)</td>
<td>1</td>
</tr>
<tr>
<td>4 (16.2 to 42.5)</td>
<td>3</td>
</tr>
<tr>
<td>Third-trimester blood lead (µg/dl)</td>
<td></td>
</tr>
<tr>
<td>1 (0.4 to 1.2)</td>
<td>3</td>
</tr>
<tr>
<td>2 (1.3 to 1.7)</td>
<td>3</td>
</tr>
<tr>
<td>3 (1.8 to 2.7)</td>
<td>2</td>
</tr>
<tr>
<td>4 (2.8 to 30.0)</td>
<td>3</td>
</tr>
<tr>
<td>Postpartum blood lead (µg/dl)</td>
<td></td>
</tr>
<tr>
<td>1 (0.2 to 1.6)</td>
<td>6</td>
</tr>
<tr>
<td>2 (1.7 to 2.2)</td>
<td>10</td>
</tr>
<tr>
<td>3 (2.3 to 3.2)</td>
<td>5</td>
</tr>
<tr>
<td>4 (3.3 to 25.4)</td>
<td>7</td>
</tr>
</tbody>
</table>
None of these attempts revealed a significant omitted variable or a variable whose presence or absence significantly altered the inverse blood lead–blood pressure association.

**Significance**

The increased risk of hypertension associated with increased bone lead in pregnant women is small. However, given the prevalence of hypertension during pregnancy, the past lead exposure of a population will significantly increase the underlying rate of hypertension.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change in blood pressure (mmHg)</th>
<th>Third trimester</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Systolic pressure</td>
<td>Diastolic pressure</td>
</tr>
<tr>
<td></td>
<td>(\beta)</td>
<td>95% CI†</td>
<td>(\beta)</td>
</tr>
<tr>
<td>Natural log blood lead ((\mu g/dl))‡</td>
<td>–0.04</td>
<td>–1.26, 1.18</td>
<td>0.20</td>
</tr>
<tr>
<td>Tibia lead (10 (\mu g/g))</td>
<td>0.07</td>
<td>–0.62, 0.77</td>
<td>0.18</td>
</tr>
<tr>
<td>Calcaneus lead (10 (\mu g/g))</td>
<td>0.70</td>
<td>0.04, 1.36</td>
<td>0.54</td>
</tr>
</tbody>
</table>

* Data were adjusted for postpartum hypertension, education, immigrant status, current smoking, current alcohol use, parity, age, and body mass index.
† CI, confidence interval.
‡ Conversion: 10 \(\mu g/dl\) = 0.483 \(\mu mol/liter\).

Women with low present lead exposure may have elevated bone lead levels due to past lead exposure and thus increased risk of hypertension during pregnancy. Prevention of lead exposure during a woman’s entire reproductive life may be required in order to reduce lead-associated health risks to the mother and fetus during pregnancy. In the context of documented histories of population lead exposure, these results also suggest that the full impact of the current low exposures to lead in the United States and much of the developed world on population health will not be felt for years, or even longer in countries just starting to implement lead reduction programs.

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**FIGURE 2.** Partial residual plots of calcaneus lead concentration versus third-trimester systolic blood pressure from the model shown in table 4 (\(n = 668\)), King-Drew Medical Center prenatal care clinics, Los Angeles, California, 1995–2001. An increase in calcaneus lead concentration from the fifth percentile to the 95th percentile in the sample (from –7.9 \(\mu g/g\) to 29.7 \(\mu g/g\)) was associated with an increase of 2.6 mmHg in prenatal systolic blood pressure. The solid line shows the best-fitting linear partial regression.

**FIGURE 3.** Partial residual plot of postnatal blood lead concentration versus postnatal diastolic blood pressure from the model shown in table 4 (\(n = 668\)), King-Drew Medical Center prenatal care clinics, Los Angeles, California, 1995–2001. Note the natural log scale of blood lead on the x-axes. The upper x-axis is labeled with natural log lead values, and the lower x-axis is labeled with untransformed lead values. The solid line shows the best-fitting linear partial regression.
ACKNOWLEDGMENTS

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